Primary Care; Clinics in Office Practice
Volume 31 • Number 3 • September 2004

Review article

Clinical application of genetic risk assessment strategies for coronary artery disease: genotypes, phenotypes, and family history

Maren T. Scheuner, MD, MPH

Department of Health Services
University of California Los Angeles School of Public Health
650 Charles E. Young Drive
South Room 31-269
Los Angeles, CA 90095-1772, USA

E-mail address: scheuner@ucla.edu

This article was supported in part by a Career Development Award sponsored by the Centers for Disease Control and Prevention and the Association of Teachers of Preventive Medicine.
PII S0095-4543(04)00044-2

Coronary artery disease (CAD) is the leading cause of death and premature disability in the United States and other industrialized countries [1] . Individuals with **genetic** predisposition to atherosclerosis have substantial **risk** for developing CAD, especially at early ages [2] . As a result, they may have the most to gain from preventive interventions [3] . This article reviews the role of **genetics** in the development and progression of CAD; available **genetic risk** assessment strategies for CAD; and **clinical application of genetic risk** information for CAD prevention, including recommendations for **risk** factor modification and early detection and the role of **genetic** counseling and education.

1. Role of genetics in development and progression of coronary artery disease

The accumulation of atherosclerotic plaque in an artery wall is a chronic disease that begins early in life [4] . This process seems to be initiated or facilitated by chronic injury to the endothelium [5] . Plaques may become symptomatic when they are large enough to restrict blood flow, leading to tissue ischemia. Acute coronary syndromes, such as unstable angina, myocardial infarction (MI), and sudden death, occur when thrombus forms on a thrombogenic plaque or when unstable plaques rupture or ulcerate leading to thrombus formation and possible vessel occlusion [6] [7] .

CAD is a complex disorder resulting from many **risk** factors. Multiple biochemical processes are involved, including lipid and apolipoprotein metabolism, inflammatory response, endothelial function, platelet function, thrombosis, fibrinolysis, homocysteine metabolism, insulin sensitivity, and blood pressure regulation [2] . Each of the biochemical processes associated with CAD comprises enzymes, receptors, and ligands, which are encoded by genes. Variations in these genes can alter the function of the constituents within a metabolic pathway. These **genetic** variations interact with each other and with nongenetic factors, resulting in variable susceptibility to the development and progression of atherosclerosis and thrombosis [2] . Nongenetic **risk** factors for CAD include exposures, such as tobacco smoke, and behaviors (eg, exercise and dietary patterns), many of which may be culturally determined. Similar to **genetic** factors, environmental and behavioral **risk** factors often aggregate in families.

Dozens of candidate genes have been associated with CAD or MI [8] , although some associations have conflicting results (eg, angiotensin-converting enzyme, methylenetetrahydrofolate reductase [MTHFR], platelet glycoprotein receptor IIIa, and factor VII) [9] [10] [11] [12] [13] [14] [15] [16] [17] [18]). The variable results may be due to chance; to errors in estimating the frequency of polymorphisms in the case or control group; to not matching the race/ethnicity of cases and controls; or to studying related but distinct phenotypes, such as the presence of atherosclerosis versus the occurrence of MI. Investigations using genome scan approaches have found novel **genetic** loci associated with CAD, which might provide additional insight to **genetic** factors contributing to atherosclerosis and coronary events [19] [20] [21] [22] [23] . There also are numerous studies that have found **genetic** associations or linkage with related disorders, such as hypertension [24] [25] [26] [27] [28] [29] , obesity [30] [31] [32] [33] [34] [35] [36] [37] [38] , diabetes [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] , lipids [50] [51] [52] [53] , and oxidative stress [54] .

2. Genetic risk assessment strategies to assess coronary artery disease and myocardial infarction susceptibility

CAD is a complex disorder. Generally the manifestations of CAD arise from the interaction of several predisposing **genetic** or environmental factors. Global **risk** assessment has been recognized as an effective approach in preventing CAD and its manifestations [55] . Through global **risk** assessment, a more accurate estimation of absolute **risk** can be determined based on the summation of **risks** contributed by each **risk** factor. Subsequently the intensity of managing modifiable **risk** factors can be adjusted by the severity of the overall **risk**.

Most people are served well by existing global **risk** assessment methods and prevention guidelines. **Genetic** susceptibility to CAD is not addressed adequately by these methods, however, and underestimation of **risk** and missed opportunities for prevention can result for people who are genetically predisposed to CAD. The Framingham **Risk** Score is a widely used **risk** assessment method for prediction of CAD **risk** [56] . It considers the established **risk** factors of gender, age, smoking, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and diabetes, but not family history of CAD or related disorders. The National Cholesterol Education Program Expert Panel [57] provides algorithms for treatment of lipid disorders in adults. The established **risk** factors of hypertension, diabetes, smoking, gender, age, and minimal family history information (parental history of MI before age 55) are used to determine **risk** and recommend lipid-lowering treatment. The **risk** associated with additional family history of CAD or related disorders is not included, however.

2.1 Family history collection and interpretation

The systematic collection and interpretation of family history information is currently the most appropriate screening approach to identify individuals with **genetic** susceptibility to CAD and MI. Family history of CAD and related conditions reflects the interactions of **genetic**, environmental, cultural, and behavioral **risk** factors shared among family members.

Family history of CAD is a significant **risk** factor for CAD. On average, there is a two to three fold increase in **risk** for CAD in first-degree relatives of affected individuals [58] [59] [60] [61] [62] . Having two or more first-degree relatives with CAD is associated with a three to six fold increase in **risk** [63] [64] . The earlier the age of onset, the greater is the **risk** of CAD to relatives [63] [64] [65] [66] . In addition, the **risk** of disease is typically greater in relatives of female cases compared with male cases, suggesting greater **genetic** burden in female cases [61] [66] [67] [68] .

Much of the familial aggregation of CAD might be explained by the familial aggregation of established **risk** factors, such as elevated LDL cholesterol, low HDL cholesterol, and diabetes [66] . In an analysis of the Third National Health and Examination Survey, adults with a parental history of CAD were more likely to have multiple **risk** factors (odds ratio [OR] for four or five **risk** factors compared with none = 2.9, 95% confidence interval [CI], 1.4–6.3) [66] . Even after adjusting for these established **risk** factors, the family history remains a significant independent **risk** factor for CAD [65] [66] [68] [69] [70] [71] [72] [73] [74] [75] . An explanation for this remaining **risk** may be familial aggregation of emerging CAD **risk** factors, including hyperhomocysteinemia [76] ; C-reactive protein (CRP) [77] ; elevated fibrin D-dimer, tissue plasminogen activator, and fibrinogen [78] ; and insulin resistance [79] . In addition, the interactions of the **genetic**, environmental, cultural, and behavioral **risk** factors shared by family members may be too complex to assess with usual statistical methods.

The estimated accuracy and prevalence of a family history of CAD and related disorders are high enough to justify using family history for **risk** stratification and targeting screening and prevention to the level of familial **risk**. Several studies have shown that family history reports of CAD in first-degree relatives are generally accurate with sensitivity estimates of 67% to 85% [63] [80] [81] . The relatively high sensitivity values indicate that family history can be used with some confidence to stratify **risk** above average. The specificity estimates for family history reports are more than 90% [63] [80] [81] , indicating a lack of overreporting disease in relatives. Similar sensitivity and specificity estimates are seen for diabetes and hypertension [81] . Prevalence rates of a positive family history of CAD are substantial, with estimates ranging from 14% among high school students [82] to 29% among healthy adults in their mid-30s (11% having a high familial **risk** and 18% having an intermediate familial **risk**) [83] .

Individuals with familial **risk** for CAD can be identified by asking targeted family history questions, including the number of relatives affected with CAD; their age at diagnosis; their gender; their degree of relationship to each other and the patient; and the presence of other conditions in the family, such as stroke, hypertension, lipid abnormalities, and diabetes [83] . With this information, stratification into different familial **risk** groups is possible, which can inform prevention activities [83] . Pedigree analysis, which involves collection and interpretation of more comprehensive family medical history, is performed in a **genetic** evaluation for individuals with high familial **risk** of CAD or for individuals who may have mendelian forms of cardiovascular disease.

2.2 Biochemical testing to assess coronary artery disease and myocardial infarction susceptibility

Tests to assess **genetic risk** for CAD are primarily biochemical analyses that measure the different pathways involved in development and progression of coronary atherosclerosis. Several of these tests identify established **risk** factors, such as increased LDL cholesterol, decreased HDL cholesterol, and diabetes, which are known to be causally related to CAD [55] . Many others are considered emerging **risk** factors, which are strongly associated with CAD [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] , but for most a causal relationship with CAD has not been determined. Examples of emerging **risk** factors for CAD include small dense LDL particles, hyperhomocystinemia, CRP, interleukin-6, and factors involved in fibrinolysis such as plasminogen activating factor inhibitor-1 and fibrinogen. Although treatment strategies exist for many emerging **risk** factors (see later), treatment for most of them so far has not been associated with primary prevention of CAD events. Nonetheless, measuring these **risk** factors can result in more accurate **risk** stratification. Currently, recognizing a higher level of CAD **risk** because of emerging **risk** factors allows patients and clinicians the opportunity to intensify the treatments that have been proved effective for CAD prevention.

Hyperhomocysteinemia

Extreme elevations in plasma homocysteine (>200 μmol/L), owing to deficiency of cystathionine β-synthase or other key enzymes involved in homocysteine metabolism, cause premature cardiovascular disease. More modest elevations of homocysteine (>10 to 15 μmol/L) are associated with increased **risk** for cardiovascular disease [93] . Homocysteine may increase the **risk** for cardiovascular disease by decreasing endothelium-dependent vasodilation, increasing platelet adhesiveness, activating certain clotting factors, and inhibiting fibrinolysis by promoting lipoprotein(a) binding to fibrin [94] . Homocysteine levels are increased by deficiency of the B vitamins that are cofactors for enzymes involved in homocysteine metabolism, including folic acid and vitamins B_6 and B_{12}. Homocysteine also increases with declining renal function, pernicious anemia, thyroid dysfunction, psoriasis, certain malignancies, anticonvulsant therapies, certain oral contraceptives, methotrexate, niacin, fibrates, and metformin [95] [96] . Homocysteine levels often can be lowered to a desirable range with folic acid and vitamins B_6 and B_{12} [97] [98] [99] . Lowering homocysteine with B vitamins was shown to decrease the incidence of major cardiovascular events in a double-blind, placebo-controlled trial in 533 subjects with coronary stenosis [100] . Another trial comparing high-dose versus low-dose B vitamins in 3680 patients with ischemic stroke [101] and a controlled trial of folate alone for patients with CAD [102] showed no effect of vitamin supplementation on subsequent coronary events or stroke, even though baseline homocysteine levels were associated with increased **risk** in these prospective studies. The preventive effect of vitamins *before* development of symptomatic atherosclerosis is unknown.

Lipoprotein(a)

Lipoprotein(a) is a lipoprotein particle composed of an apolipoprotein B-100 particle covalently linked to an apolipoprotein(a) particle. Apolipoprotein(a) is homologous to plasminogen and may compete with plasminogen, limiting fibrinolysis [103] . Lipoprotein(a) also has been implicated in foam cell formation, endothelium-dependent vasodilation reduction, and LDL cholesterol oxidation promotion [104] . Levels of lipoprotein(a) are strongly genetically determined [105] [106] . Lipoprotein(a) increases slightly with age and at the time of acute illness; also, females have greater values than males, with values increasing after menopause [107] . The distribution of levels varies widely among racial and ethnic groups [107] . Most of the associations with CAD have been found in white. Levels greater than 20 to 30 mg/dL are considered high. Lipoprotein(a) levels can be reduced with niacin [108] . Diet and exercise have no effect on lipoprotein(a) levels [109] [110] . In postmenopausal women, estrogen replacement therapy can lower levels [111] , and in men, testosterone can lower levels [112] . Reduction in lipoprotein(a) attributed to estrogen has been associated with a reduction in cardiovascular events in women [113] . Hormone replacement therapy (HRT) with either estrogen for women or testosterone for men is not the standard of care for reducing CAD **risk**, however. Aggressive LDL cholesterol lowering seems to abolish the CAD **risk** associated with elevated lipoprotein(a), even with unchanged lipoprotein(a) levels [114] . LDL cholesterol lowering should be the treatment goal for high-risk individuals with elevated lipoprotein(a).

Atherogenic lipoprotein phenotype

Atherogenic small, dense LDL cholesterol particles, reduced fraction of HDL2b, low HDL cholesterol, elevated triglycerides, and excess apolipoprotein B are characteristic of the atherogenic lipoprotein phenotype (ALP). ALP occurs in 25% of middle-aged men [115] and is associated with a threefold increase in CAD **risk** [116] [117] . ALP can be improved with regular exercise, loss of body fat, restricted intake of simple carbohydrates and alcohol [118] , medical therapy including niacin and fibrates [119] [120] , and avoidance of β-blockers if possible [121] . Fish oil supplementation also improves the lipid profile associated with ALP [122] . Modifying ALP with the aforementioned measures, particularly niacin alone or in combination with other lipid-lowering therapy, has resulted in regression or prevention of progression of coronary atherosclerotic lesions and reduced coronary **risk** [123] .

Insulin resistance

Insulin resistance is associated with many traditional and emerging **risk** factors (hypertension, hypertriglyceridemia, small LDL cholesterol particles, decreased HDL cholesterol, elevated plasminogen activator inhibitor-1, fibrinogen, and CRP). It can be considered a **risk** factor predisposing to CAD [55] . An estimated 24% of adults in the United States have the metabolic syndrome associated with insulin resistance [124] . The third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [57] highlighted the importance of treating patients with the metabolic syndrome to prevent cardiovascular disease. Insulin resistance can be treated effectively with lifestyle changes and metformin [125] .

C-reactive protein

Many studies have shown a strong association between CRP and future cardiovascular events [126] [127] . Measurement of high-sensitivity CRP (hs-CRP) is a useful **clinical** marker of inflammation related to atherosclerosis [127] . Statin drugs used for cholesterol lowering have been associated with reduction in hs-CRP [128] . This reduction may be due in part to the anti-inflammatory effects of these drugs. A report has shown that HRT increases CRP levels [92] , suggesting a possible mechanism for increased CAD **risk** due to HRT. hs-CRP could become a target of therapy for reducing CAD **risk**. At this time, measurement of hs-CRP is used primarily to stratify **risk** and guide recommendations for modification of other **risk** factors.

Thrombophilia

Several factors involved in promotion of thrombosis and inhibition of fibrinolysis are associated with CAD. (See the article by Feero in this issue for a review of inherited thrombophilias predisposing to venous thrombosis.) Among this group of CAD **risk** factors, fibrinogen is one of the most important. Fibrinogen levels are modifiable through smoking cessation, aerobic exercise, weight loss, fibric acid medications, and omega-3 fish oils [129] [130] . Antiplatelet medications, such as aspirin and other forms of anticoagulants, also might reduce the thrombotic **risk** associated with elevated fibrinogen.

2.3 DNA-based testing to assess susceptibility to coronary artery disease and myocardial infarction

There are more than 30 mendelian disorders (single-gene disorders) that feature CAD or MI (Table 1) [131] . **Genetic** tests for many of these mendelian disorders are available and include DNA-based tests and biochemical analyses [132] . These conditions generally are associated with a substantial **risk** for CAD and MI at young ages. For most of these mendelian disorders, personal and family history characteristics are crucial for identifying individuals at **risk**. Specifically, early-onset CAD is usually present in multiple family members, and family members may have associated conditions, such as stroke, diabetes, thrombophilia, or cholesterol abnormalities. Collection and interpretation of family medical history is central to providing access to **genetic** testing services that are available for diagnosis of mendelian forms of CAD and MI.

Table 1. Mendelian disorders featuring coronary artery disease and myocardial infarction

Disorder	Mode of inheritance	OMIM entry*
Abdominal obesity-metabolic syndrome	MF	605552
Apolipoprotein (a) polymorphism/lipoprotein A excess	AD	152200.0001
Apolipoprotein A-I deficiency	AD, AR	107680.0011
		107680.0012
		107680.0013
		107680.0015
		107680.0017
		107680.0022
Atherosclerosis susceptibility/atherogenic lipoprotein phenotype (ALP)	AD, MF	108725
Coronary artery dissection, spontaneous	AD	122455
Cerebrotendinous xanthomatosis	AR	213700
Fabry disease	XLR	301500
Familial combined hyperlipidemia	AD, MF	144250
Familial defective apo B	AD	144010
Familial hypercholesterolemia	AD	143890
Familial hypercholesterolemia, autosomal recessive	AR	603813
Familial partial lipodystrophy	AD	151660
Familial pseudohyperkalemia due to red blood cell leak	AD, AR	177720
Fibromuscular dysplasia of arteries	AD	135580
Heparin cofactor II deficiency	AD	142360
Homocysteinemia	AD, MF	603174
Homocystinuria	AR	236200
Homocystinemia/homocystinuria due to 5,10 methylenetetrahydrofolate reductase deficiency	AR	236250
Hyperlipoproteinemia, type III	AR with pseudodominance	107741
Methylcobalamin deficiency, cbl G type	AR	250940
Niemann-Pick disease, type E	AR	257200
Progeria	AD	176670
Protein C deficiency	AD	176860

Pseudoxanthoma elasticum	AR	264800
Pseudoxanthoma elasticum, autosomal dominant	AD	177850
Sitosterolemia	AR	210250
Spontaneous coronary dissection	AD	122455
Tangier disease	AR	205400
Vitamin B_{12} metabolic defect, type 2	AR	277410
Vitamin B_{12} metabolic defect with methylmalonic acidemia and homocystinuria	AR	277400
Werner's syndrome	AR	277700
Williams syndrome	AD	194050

* OMIM, On-line Mendelian Inheritance in Man [132] , a periodically updated reference to inherited disorders associated with alterations in single genes.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MF, multifactorial; XLR, X-linked recessive.*Data from:* Scheuner MT. **Clinical application of genetic risk** assessment strategies for coronary artery disease. Genet Med 2003;5:269–85.

Despite the success of identifying susceptibility genes for multifactorial, nonmendelian forms of CAD and associated conditions, the **risk** associated with any one of these gene variants is generally of small magnitude and by itself has little **clinical** significance [133] . Before testing for low-risk susceptibility genes has widespread **clinical application**, additional studies are needed to assess the prevalence and penetrance of these genotypes and the effect of other genes and environmental factors on their expression. The **clinical** utility of DNA-based testing for CAD susceptibility compared with other **risk** assessment strategies, including familial **risk** assessment and assessment of biochemical **risk** factors, must be proved. Nonetheless, testing for many CAD susceptibility genotypes is available. Subsequent examples describe the potential benefit and limitations of DNA-based testing for CAD susceptibility in the **clinical** setting.

Cholesterol ester transfer protein

Kuivenhoven et al [134] found a significant association between variation at the cholesterol ester transfer protein locus and angiographic progression of coronary atherosclerosis in men with CAD. There was a dose-dependent relationship between one specific cholesterol ester transfer protein gene polymorphism (TaqIB) and the efficacy of pravastatin in slowing the progression of atherosclerosis. Although this cholesterol ester transfer protein association with CAD progression was significant, the finding has limited **clinical** utility. Although individuals with the B1B1 genotype derived the greatest benefit, treatment with pravastatin improved the outcome for all study subjects, abolishing any differences based on cholesterol ester transfer protein genotype.

Apo E

The ApoE4 allele has been associated with CAD in several populations [135] [136] [137] . ApoE2/E2 homozygous individuals are at **risk** for type III hyperlipoproteinemia, which is associated with an increased **risk** for atherosclerosis. In addition, apoE genotyping could come to play a role in recommending lipid-lowering diets [122] [138] [139] [140] [141] . Forty percent of the individual variation in response of LDL cholesterol levels to a low–saturated fat diet is familial [142] ; this might be due in part to the apoE locus. Several studies have shown that carriers of the apoE4 allele tend to be more responsive to the LDL-lowering effects of low-fat dietary interventions compared with noncarriers [138]

[139] [140] [141] . Carriers of the apoE2 allele may be particularly susceptible to unfavorable changes in lipids and to coronary heart disease when they are exposed to diets high in saturated fat [141] .

The apoE genotype influences the responsiveness to fish oil supplementation in subjects with an ALP [122] . Individuals with an apoE2 allele displayed favorable changes when given fish oil, including a marked reduction in the postprandial increase in triglycerides and a trend toward increased lipoprotein lipase activity compared with non-apoE2 carriers [143] . ApoE4 carriers had an unfavorable response compared with E3/E3 homozygotes with a significant increase in total cholesterol and a trend toward a reduction in HDL cholesterol [122] .

Despite these important associations relating response to diet and the apoE genotype, clinicians must proceed with caution when considering this particular **genetic** test as a means to assess CAD **risk**. The apoE4 genotype also is associated with increased **risk** for Alzheimer's disease [144] . The American College of Medical **Genetics** (ACMG) and the American Society of Human **Genetics** (ASHG) have not endorsed apoE testing for diagnosis or prediction of Alzheimer's disease [145] . Testing may be harmful because individuals discovering that they may have increased **risk** for Alzheimer's disease currently do not have available clear actions for preventing the disease. Patients should be informed of the association of apoE genotype with Alzheimer's disease if considering apoE genotyping for cardiovascular disease **risk** assessment.

Methylenetetrahydrofolate reductase

Homozygosity for the MTHFR C677T mutation has been associated with elevated levels of homocysteine [146] ; homocysteine levels are associated with CAD **risk** [93] . A meta-analysis of case-control studies showed a significantly higher **risk** of CAD associated with the MTHFR C677T genotype, especially in the setting of low folate levels [147] . The ACMG/ASHG statement regarding measurement and use of total plasma homocysteine recommends that the specific basis for elevated homocysteine levels (>15 μM) be determined before treatment because inappropriate supplementation of folate, vitamin B_{12}, and pyridoxine possibly may cause harm [148] .

Prothrombin G20210A

In a study of postmenopausal women, **risk** of MI was significantly increased (OR = 10.9, 95% CI, 2.15–55.2) in women with the prothrombin G20210A mutation who also had hypertension and were taking HRT [149] . Women with the prothrombin mutation had only a mildly increased **risk** of MI if they did not use HRT. Women without the prothrombin G20210A mutation were not at substantially increased **risk** for MI, even if they used HRT. These findings suggest a potential benefit of prothrombin G20210A mutation testing in women at high **risk** for MI who are considering use of HRT. Decision making regarding HRT use is complex, however, and it is uncertain how much value such testing would add in the **clinical** setting.

Platelet glycoprotein Ia/IIa receptor

Smoking is a significant **risk** factor for CAD and MI. Individuals with specific genotypes have greater **risks** for MI, however, associated with smoking. One example is the Gln-Arg192 polymorphism of the human paraoxonase gene [150] . Another is the 807T allele of the platelet glycoprotein Ia/IIa receptor [151] . Homozygosity for the platelet glycoprotein Ia/IIa receptor 807T by itself is associated with about a threefold increase in **risk** for MI; smoking alone is associated with a fourfold increase in **risk** [151]. These two **risk** factors interact with a greater than multiplicative effect, yielding an OR of 25 for MI among individuals who are homozygous for the 807T allele and also smoke [151]. Although knowledge of increased **risk** due to high-risk alleles might be expected to improve smoking cessation efforts, this has not been shown. The absence of these **risk** alleles does not allow one to smoke with impunity because smoking likely increases **risk** for MI through other mechanisms, and it is associated with other hazardous health effects.

Platelet glycoprotein IIIa receptor

Several studies have identified a strong association between the platelet glycoprotein receptor IIIa A2 allele and extensive CAD or occurrence of coronary thrombosis [12] [13] [14]. Other studies have failed to show an association, however, with CAD or MI [15] [16] [17]. Cooke et al [18] argued that differences in aspirin use might account for some of the discrepancies in studies investigating this polymorphism because aspirin has been shown to inhibit the increased platelet aggregation observed with this polymorphism. Aspirin likely has other beneficial effects in the prevention of CAD and acute coronary syndromes. Its use is recommended for primary and secondary prevention of CAD [152]. The **clinical** utility of genotyping glycoprotein receptor IIIa would be limited because it seems unlikely that this test alone would distinguish who would benefit from chemoprevention with aspirin.

5-Lipoxygenase polymorphisms

5-Lipoxygenase converts dietary fatty acids to leukotrienes, potential inflammatory mediators of atherosclerosis. In a cross-sectional study of 470 healthy, middle-aged people, carotid artery intima-media thickness (measured as a marker of atherosclerosis) was increased in the 6% of people with a variant genotype (either of two polymorphisms) in the promoter region of the 5-lipoxygenased gene [153]. The increased thickening, adjusted for other **risk** factors, was comparable to the increase seen with diabetes. People with these polymorphisms also had doubled levels of CRP. Higher dietary intake of polyunsaturated n-6 fatty acid increased the effect of the gene variant, whereas higher intake of n-3 fatty acids (eg, from fish oils) lessened the effect [153]. Although this observation suggests a genotype-diet interaction that could identify people more likely to respond to fish oils for prevention of atherosclerosis, **clinical** use of 5-lipoxygenase genotyping would have to await prospective studies showing that individualized treatment prevents CAD.

α-Adducin variant

A population-based, case-control study of patients treated for hypertension found a significant interaction between the α-adducin gene variant, Trp460, and diuretic therapy in the **risk** of MI or stroke [154]. The α-adducin gene variant was identified in more than one third of the participants. The **risk** of MI or stroke in individuals with the wild-type genotype did not depend on the type of antihypertensive therapy. In carriers of the α-adducin variant, however, diuretic therapy was associated with a lower **risk** of MI and stroke than other antihypertensive therapies (OR = 0.49; 95% CI, 0.32–0.77). Other traditional cardiovascular disease **risk** factors did not influence this interaction. These results suggest a role for genotyping hypertensive individuals for the α-adducin variant allele, Trp460, to determine benefit from diuretic therapy. These findings need to be confirmed in other studies, however, and other benefits and **risks** of diuretic therapy need to be considered before such testing translates to **clinical** practice.

Alcohol dehydrogenase type 3

Alcohol consumption has been associated with reduced **risk** of CHD. People with an alcohol dehydrogenase type 3 allele metabolize alcohol more slowly. This **genetic** variant in men also is associated with a lower **risk** of MI (relative **risk** [RR] = 0.65; 95% CI, 0.43–0.99) [155] . A significant interaction between this allele and alcohol intake has been found. People who are homozygous for this allele and drink at least one drink a day have the greatest reduction in **risk** for MI (RR = 0.14; 95% CI, 0.04–0.45) and the highest HDL cholesterol levels (for interaction $P = .05$). This finding has limited **clinical** utility because all men in this study seemed to benefit from consuming at least one drink per day regardless of their genotype. In addition, many other variables need to be considered when counseling about alcohol intake.

Estrogen receptor-α gene

Herrington et al [156] showed that sequence variation of the estrogen receptor-α gene (IVS1-401 C/C genotype) is associated with the magnitude of increase in HDL cholesterol levels when estrogen or combination HRT is administered to women with CAD. This response has not been linked yet to variation in the **risk** of cardiovascular disease, however.

3. Approach to individuals with high familial risk

This section reviews the process of **genetic** evaluation for an individual referred because of personal or family history characteristics suggesting a strong **genetic** susceptibility to CAD or MI (Box 1). The process includes (1) **genetic** counseling and education; (2) **risk** assessment using personal and family medical history, physical examination, laboratory testing, and screening for early detection of CAD; and (3) recommendations for **risk** factor modification.

Box 1. Characteristics of genetic susceptibility to coronary artery disease (CAD)

Consultation for **genetic risk** assessment and specialized **risk** reduction should be considered for individuals with at least one of the following characteristics:

- Early-onset CAD, men age <55 and women age <65
- More than one close relative[a] with CAD, especially female relatives
- Multiple atherosclerotic vessels (eg, coronies, carotids, aorta) with multifocal involvement (ie, angiographic severity)
- Presence of multiple CAD **risk** factors in family members with CAD
- Presence of related disorders in close relatives (eg, diabetes, stroke, hypertension, peripheral vascular disease)

[a]Close relative, first- or second-degree relative from the same lineage.

3.1 Genetic counseling and education regarding coronary artery disease susceptibility

An important goal of **genetic** evaluation for CAD is the development of individualized preventive strategies based on the **genetic risk** assessment and the patient's personal medical history, lifestyle, and preferences. **Genetic** counseling is crucial for delineating a patient's motivation and likely responses to learning of a **genetic risk**. Through **genetic** consultation, patients are educated about the role of behavioral and **genetic risk** factors for CAD, their mode of inheritance, and the options for prevention and **risk** factor modification. This communication process ensures the opportunity to provide informed consent, including discussion of the potential benefits, **risks**, and limitations of **genetic risk** assessment and options for prevention [157] .

Although family history of CAD has been shown to be a significant predictor of CAD **risk**, a report has shown that this familial **risk** does not translate into spontaneous improvement in lifestyles of at-risk relatives [158] . In the Coronary Artery **Risk** Development in Young Adults (CARDIA) study, CAD **risk** factors were assessed over two consecutive 5-year follow-up periods among 3950 participants aged 18 to 30 years. Kip et al [158] found that the occurrence of a heart attack or stroke in a young adult's immediate family member did not lead to self-initiated, sustained change in modifiable **risk** factors. These results argue that primary care clinicians may need to intervene actively with people with a family history of CAD, in whom the opportunities for prevention are substantial [3] .

Because most of the established and emerging **risk** factors for CAD aggregate in families, a family-based approach to **risk** factor modification ought to be an effective strategy, and this has been shown in a few studies [159] [160] [161] . Lifestyle changes, such as dietary modification, weight control, and smoking cessation, are likely to be more effective when delivered to the family than to an individual because family members can influence each other and provide ongoing support to one another.

3.2 Risk assessment

Review of the personal medical history should include diagnoses of CAD, MI, peripheral vascular disease, stroke (including transient ischemic attacks), thrombosis, arrhythmia, heart failure, pulmonary disease, diabetes, and hypertension. Medical records, particularly procedure reports, are reviewed for confirmation. The review of systems focuses on cardiorespiratory function, including questions regarding angina, shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, pedal edema, claudication, and exercise tolerance. Inquiry regarding tobacco exposure, history of alcohol use, exercise, and diet also should be performed.

During **genetic** consultation, a pedigree is constructed by obtaining demographic and medical information for all first-degree and second-degree relatives, including current age or age at death; cause of death if deceased; history of CAD, other forms of heart disease, and related conditions such as stroke, peripheral vascular disease, aortic aneurysm, hypertension, diabetes, and lipid abnormalities; and associated **risk** factors, such as smoking. Additional questioning can be helpful regarding procedures that might have been performed, such as coronary artery bypass surgery, angioplasty, echocardiogram, or pacemaker placement. When available, medical records and autopsy reports of family members are reviewed to verify diagnoses and document test results. The family history should include ethnicity and country of origin because certain conditions might be more prevalent in certain ethnic groups. The prevalence of insulin resistance is high among individuals of Native American admixture [162] [163] .

When this information is collected, pedigree analysis is performed to determine the most likely mode of inheritance (ie, mendelian versus multifactorial) and the **risk** of disease to the patient and to unaffected relatives. If a mendelian disorder is suspected, this analysis helps to elucidate the differential diagnosis. This process can inform recommendations for appropriate diagnostic tests and individualized management and prevention strategies.

An inherited susceptibility to thrombosis may be suspected in a pedigree that features multiple affected relatives with early onset of CAD, stroke, and other thromboembolic events [164] . Testing of thrombotic markers might reveal important **risk** factors in the family. Recommendations can be made to avoid factors that may aggravate that **risk**, such as use of oral contraceptives, HRT, and prolonged periods of immobility, and for prophylactic use of anticoagulants in high-risk situations. (See Feero article in this issue.)

A physical examination focused on CAD **risk** should include blood pressure in the arms and the ankles. In addition to identifying hypertension, these measurements can be used to calculate the ankle/brachial blood pressure index (ABI). ABI values less than 0.9 are correlated with atherosclerosis. In addition, a blood pressure of 130/85 mm Hg or greater is a criterion for the metabolic syndrome [57] . Weight and height should be obtained, and body mass index should be calculated. Theses data can be helpful in identifying a need for achieving an ideal weight and monitoring diet and exercise interventions. Waist circumference should be obtained because it can be a factor in identifying the metabolic syndrome [57] . Evaluation of lipid disorders should include examination of the eyes, assessing corneal arcus and lipemia retinalis. Examination of the skin should include assessment for xanthelasma and tendinous xanthomas. The cardiovascular examination should include careful assessment of the heart and lungs; listening for bruits at major vessels in the neck, abdomen, and groin; and palpation of the aorta and distal pulses. Any abnormalities can be followed up with additional studies, such as ultrasound. Physical signs of mendelian disorders that feature cardiovascular disease (eg, Marfan syndrome, Ehlers-Danlos syndrome type IV, pseudoxanthoma elasticum, and Fabry's disease) also should be sought.

Laboratory testing to detect traditional and emerging **risk** factors for CAD includes fasting lipid panel, lipoprotein(a), LDL cholesterol particle size, HDL cholesterol fractionation, apolipoprotein B, hs-CRP, glucose, and homocysteine measurements. The atherogenic lipoprotein phenotype can be identified if there is a preponderance of small dense LDL cholesterol, decreased fraction of HDL2b (<15%), elevated triglycerides, and elevated apolipoprotein B. ALP can be treated effectively with lifestyle changes or medications (niacin or fibrates) as reviewed earlier [118] [119] [120] . Fasting insulin can be checked if there is evidence of impaired glucose tolerance. The metabolic syndrome can be identified if at least three of the following criteria are met: blood pressure 130/85 mm Hg or greater, waist circumference greater than 102 cm in men and greater than 88 cm in women, HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women, and triglycerides 150 mg/dL or greater [57] . If the metabolic syndrome is present or if there are signs of insulin resistance or impaired glucose tolerance, oral glucose tolerance testing should be considered for detection of diabetes.

DNA-based testing may be considered in specific situations for high-risk individuals. MTHFR mutation analysis for the C677T allele can be performed if hyperhomocysteinemia is detected. Factor V Leiden mutation analysis can be performed for premenopausal women with other high-risk factors for MI who are considering use of oral contraceptives. If the Factor V Leiden mutation is identified, oral contraceptives may be avoided because of an associated **risk** for MI in premenopausal women [164] . Prothrombin G20210A mutation analysis can be considered for high-risk, postmenopausal women considering HRT. The combination of HRT and the G20210A mutation is associated with **risk** for MI [149] . ApoE genotyping can be considered if there is a question about the diagnosis of type III hyperlipoproteinemia or if the apoE genotype would influence dietary recommendations significantly.

Early detection strategies for CAD might be useful to stratify **risk** further in asymptomatic individuals at increased **risk** for CAD [55] , especially if the identification of subclinical atherosclerosis would alter recommendations regarding **risk** factor modification or adherence to risk-reducing strategies. Noninvasive tests, such as carotid artery duplex scanning to measure intima-media thickness, ABI, electron-beam CT (EBCT) to detect coronary artery calcification, ultrasound-based endothelial function studies, MRI techniques, and testing for hs-CRP, offer the potential for measuring and monitoring atherosclerosis in asymptomatic people. Several of these methods are highly valid and predictive of CAD events (eg, ABI, carotid intima-media thickness, and EBCT) [55] . When a higher **risk** is confirmed with these methods, aggressive medical therapies for primary prevention can be recommended.

The EBCT is the most popular of these early detection methods. There is consistent evidence that coronary calcification correlates with the presence and degree of plaque at autopsy, by intravascular ultrasound [165] , and by angiography [166] [167] . Coronary calcification also is correlated with nonfatal MI and need for subsequent coronary revascularization in asymptomatic individuals [168] [169] [170] and patients undergoing coronary angiography [171] . A prospective study has shown that EBCT identifies a high-risk group of asymptomatic subjects with clinically important silent ischemia as shown by stress myocardial perfusion single-photon emission CT (SPECT) [172] . Abnormal SPECT was seen in 11.3% of patients with coronary calcium scores of 101 to 399 and 46% with scores of 400 or greater. Until more recently, however, the added value of the coronary calcium score beyond the usual **risk** assessment methods had not been shown. In a study of sibships at high **risk** for hypertension, a coronary artery calcium score above the 70th percentile was significantly associated with occurrence of coronary events, over an average of 5 years, after adjusting for Framingham **Risk** Scores (OR = 2.8; 95% CI, 1.2–6.4) [173] . For individuals with a greater than average CAD **risk** (eg, people with a significant family history), the coronary calcium score obtained with EBCT has potential to detect advanced but asymptomatic coronary atherosclerosis, leading to recommendations for aggressive **risk** factor modification. At least one study has shown that knowledge of coronary calcium scores positively influenced behavior in self-referred subjects [174] , although additional outcomes research regarding the utility of this approach is necessary. In addition, low coronary calcium scores may be valuable in defining a lower CAD **risk** [55] , which could provide some reassurance to individuals assigned a high **risk** because of their family history. **Risk** factor modification could be relaxed some for them, on the basis of EBCT.

3.3 Risk factor modification

Genetic information about CAD **risk** has value in guiding decision making regarding lifestyle and other disease management and prevention strategies. Individuals with a strong **genetic** susceptibility to CAD, as determined by family history and the presence of established and emerging **risk** factors, may derive the greatest benefit from traditional preventive strategies, such as smoking cessation and screening and treatment for elevated cholesterol and blood pressure. Individuals with CAD also might benefit from targeting emerging **risk** factors with specific interventions and lifestyle changes. For the most part, however, evidence regarding primary prevention of **clinical** cardiovascular events in individuals who have modified emerging **risk** factors effectively is lacking, and prospective **clinical** trials are necessary. It is crucial to discuss these potential benefits and limitations with any patient undergoing assessment of emerging CAD **risk** factors.

Cholesterol lowering is an important **clinical** strategy in primary and secondary prevention of CAD [57] . Use of cholesterol-lowering agents has been effective in reducing atherosclerosis incidence, disease progression, and CAD mortality [174] [175] [176] [177] [178] [179] [180] . In high-risk individuals, hypercholesterolemia should be treated initially with lifestyle changes and, if necessary, with lipid-lowering medications to achieve a risk-appropriate LDL cholesterol value. Even when there is effective lipid lowering, however, a substantial proportion of individuals develop CAD or have progression of their disease [181] . Considering treatment of additional biochemical **risk** factors in high-risk individuals is a reasonable approach.

If there are small LDL cholesterol particles, niacin should be considered. Niacin can be used in combination with a statin drug if LDL cholesterol is elevated. Niacin also can be prescribed in similar doses to treat elevated lipoprotein(a) levels [108] , or if estrogen replacement therapy is an option, this can be considered [111] . Niacin also can raise HDL cholesterol [182] , as do exercise [183] and moderate alcohol intake [184] . With niacin therapy, transaminases, uric acid, and blood glucose should be monitored because abnormalities can arise [185] . Transaminases and creatinine kinase levels also can increase with statin drugs, although the usefulness of routine measurement is questionable [186] . If there is evidence of hyperhomocysteinemia, nongenetic factors should be assessed (eg, measurement of B vitamins, renal function, thyroid function, and review of medications), and B vitamin supplementation should be considered, titrating the amount of folic acid to the fasting homocysteine level [97] [98] [99] [100] . Homocysteine levels can become abnormal with niacin, fibric acid derivatives, and metformin [96] , drugs that often are used in individuals at **risk** for CAD. Insulin resistance can be treated effectively with lifestyle changes or metformin [125] .

4. Summary

Several lines of evidence support the contribution of **genetic** variations to the development and progression of CAD and to response to **risk** factor modification and lifestyle choices. Genetically predisposed individuals generally have the highest **risk** for CAD and develop disease at an earlier age. The best method to identify and stratify **genetic risk** for CAD is collection and interpretation of the family history. Additional information from the medical history, physical examination, and biochemical and DNA testing, interpreted in the context of the family history, can refine the **genetic risk** assessment further. Knowledge of **genetic** susceptibility to CAD has value in providing **risk** information and can influence lifestyle choices and management options. Genetically susceptible individuals might benefit the most from aggressive treatment of established CAD **risk** factors. In addition, many emerging **risk** factors are modifiable, and targeting these **risk** factors with specific therapies may result in improved CAD prevention. Family-based prevention might be most effective for genetically predisposed individuals because many established and emerging **risk** factors aggregate in families, and most are amenable to lifestyle changes. Early detection of CAD may be appropriate for genetically susceptible individuals to guide decision making about **risk** factor modification. Studies are needed to generate evidence regarding the feasibility, validity, and utility of using familial **risk** assessment to inform CAD prevention strategies and the ethical, legal, and social issues that may arise.

References

[1]. American Heart Association. Heart and stroke statistics: 2003 update. Dallas (TX): American Heart Association; 2002.
[2]. Scheuner MT. **Genetic** predisposition to coronary artery disease. Curr Opin Cardiol 2001;16:251-60. Abstract
[3]. Tavani A, Augustin L, Bosetti C, et al. Influence of selected lifestyle factors on **risk** of acute myocardial infarction in subjects with familial predisposition for the disease. Prev Med 2004;38:468-72. Abstract
[4]. Berenson GS, Srinivasan SR, Bao W, Newman III WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular **risk** factors and atherosclerosis in children and young adults. N Engl J Med 1998;338:1650-6. Abstract
[5]. Lefkowitz RJ, Willerson JT. Prospects for cardiovascular research. JAMA 2001;285:581-7. Abstract
[6]. Weissberg PL. Atherogenesis: current understanding of the causes of atheroma. Heart 2000;83:247. Citation
[7]. Rauch U, Osende JI, Fuster V, Badimon JJ, Fayad Z, Chesebro JH. Thrombus formation on atherosclerotic plaques: pathogenesis and **clinical** consequences. Ann Intern Med 2001;134:224-38. Abstract
[8]. Scheuner MT. **Genetic** evaluation for coronary artery disease. Genet Med 2003;5:269-85. Abstract
[9]. Ridker PM, Stampfer MJ. Assessment of **genetic** markers for coronary thrombosis: promise and precaution. Lancet 1999;353:687-8. Citation
[10]. Girelli D, Russo C, Ferraresi P, et al. Polymorphisms in the factor VII gene and the **risk** of myocardial infarction in patients with coronary artery disease. N Engl J Med 2000;343:774-80. Abstract
[11]. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of the hemostatic factors and incidence of coronary heart disease: the Atherosclerosis **Risk** in Communities (ARIC) study. Circulation 1997;96:1102-8. Abstract
[12]. Weiss EJ, Bray PF, Tayback M, et al. A polymorphism of a platelet glycoprotein receptor as an inherited **risk** factor for coronary thrombosis. N Engl J Med 1996;334:1090-4. Abstract

[13]. Carter AM, Ossei-Gerning N, Grant PJ. Platelet glycoprotein IIIa Pl^A polymorphism in young men with myocardial infarction. Lancet 1996;348:485-6. Citation

[14]. Carter AM, Ossei-Gerning N, Wilson IJ, Grant PJ. Association of the platelet Pl^A polymorphism of glycoprotein IIb/IIIa and fibrinogen beta 448 polymorphism with myocardial infarction and extent of coronary artery disease. Circulation 1997;96:1424-31. Abstract

[15]. Ridker PM, Hennekens CH, Schmitz C, Stampfer MJ, Lindpaintner K. $Pl^{A1/A2}$ polymorphism of platelet glycoprotein IIIa and **risks** of myocardial infarction, stroke, and venous thrombosis. Lancet 1997;349:385-8. Abstract

[16]. Herrmann SM, Poirier O, Marques-Vidal P, et al. The Leu^{33}/Pro polymorphism (PlA1/A2) of the glycoprotein IIIa (GPIIIa) receptor is not related to myocardial infarction in the ECTIM Study. Thromb Haemost 1997;77:1170-81. Abstract

[17]. Laule M, Cascorbi I, Stangl V, Blelecke C, et al. A1/A2 polymorphism of glycoprotein IIIa and association with excess procedural **risk** for coronary catheter interventions: a case-control study. Lancet 1999;353:708-12. Abstract

[18]. Cooke GE, Bray PF, Hamlington JD, Pham DM, Goldschmidt-Clermont PJ. Pl^{A2} polymorphism and efficacy of aspirin. Lancet 1998;351:1253. Citation

[19]. Pujukanta P, Cargill M, Viitanen L, et al. Two loci on chromosomes 2 and X for premature coronary heart disease identified in early- and late-settlement populations of Finland. Am J Hum Genet 2000;67:1481-93. Abstract

[20]. Hein L, Barsh GS, Pratt RE, Dzau VJ, Kobilka BK. Behavioural and cardiovascular effects of disrupting the angiotensin II type-2 receptor in mice. Nature 1995;377:744-7. Abstract

[21]. Harrap SB, Zammit KS, Wong ZYH, et al. Genome-wide linkage analysis of the acute coronary syndrome suggests a locus on chromosome 2. Arterioscler Thromb Vasc Biol 2002;22:874-8. Abstract

[22]. Lange LA, Lange EM, Bielak LF, et al. Autosomal genome-wide scan for coronary artery calcification loci in sibships at high **risk** for hypertension. Arterioscler Thromb Vasc Biol 2002;22:418-22. Abstract

[23]. Gudmundsson G, Matthiasson SE, Arason H, et al. Localization of a gene for peripheral arterial occlusive disease to chromosome 1p31. Am J Hum Genet 2002;70:586-92. Abstract

[24]. Bray MS, Krushkal J, Li L, et al. Positional genomic analysis identifies the beta-adrenergic receptor gene as a susceptibility locus for human hypertension. Circulation 2000;101:2877-82. Abstract

[25]. Krushkal J, Xiong M, Ferrell R, Sing CF, Turner ST, Boerwinkle E. Linkage and association of adrenergic and dopamine receptor genes in the distal portion of the long arm of chromosome 5 with systolic blood pressure variation. Hum Mol Genet 1998;7:1379-83. Abstract

[26]. Krushkal J, Ferrell R, Mockrin SC, Turner ST, Sing CF, Boerwinkle E. Genome-wide linkage analyses of systolic blood pressure using highly discordant siblings. Circulation 1999;99:1407-10. Abstract

[27]. Williams RR, Hunt SC, Hopkins PN, Wu LL, Lalouel JM. Evidence for single gene contributions to hypertension and lipid disturbances: definition, **genetics**, and **clinical** significance. Clin Genet 1994;46:80-7. Abstract

[28]. Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science 2000;289:119-23. Abstract

[29]. Frossard PM, Lestringant GG, Malloy MJ, Kane JP. Human renin gene BglI dimorphism associated with hypertension in two independent populations. Clin Genet 1999;56:428-33. Abstract

[30]. Deng H-W, Deng H, Liu Y-J, et al. A genomewide linkage scan for quantitative-trait loci for obesity phenotypes. Am J Hum Genet 2002;70:1138-51. Abstract

[31]. Lee JH, Reed DR, Li W-D, et al. Genome scan for human obesity and linkage to markers in 20q13. Am J Hum Genet 1999;64:196-209. Abstract

[32]. Heinonen P, Koulu M, Pesonen U, et al. Identification of a three-amino acid deletion in the alpha-2B-adrenergic receptor that is associated with reduced basal metabolic rate in obese subjects. J Clin Endocrinol Metab 1999;84:2429-33. Full Text

[33]. Large V, Hellstrom L, Reynisdottir S, et al. Human beta-2 adrenoceptor gene polymorphisms are highly frequent in obesity and associate with altered adipocyte beta-2 adrenoceptor function. J Clin Invest 1997;100:3005-13. Abstract

[34]. Nagase T, Aoki A, Yamamoto M, et al. Lack of association between the trp64arg mutation in the beta-3-adrenergic receptor gene and obesity in Japanese men: a longitudinal analysis. J Clin Endocrinol Metab 1997;82:1284-7. Full Text

[35]. Mitchell BD, Blangero J, Comuzzie AG, et al. A paired sibling analysis of the beta-3 adrenergic receptor and obesity in Mexican Americans. J Clin Invest 1998;101:584-7. Abstract

[36]. Sina M, Hinney A, Ziegler A, et al. Phenotypes in three pedigrees with autosomal dominant obesity caused by haploinsufficiency mutations in the melanocortin-4 receptor gene. Am J Hum Genet 1999;65:1501-7. Abstract

[37]. Ristow M, Müller-Wieland D, Pfeiffer A, Krone W, Kahn CR. Obesity associated with a mutation in a **genetic** regulator of adipocyte differentiation. N Engl J Med 1998;339:953-9. Abstract

[38]. Walder K, Norman RA, Hanson RL, Schrauwen P, et al. Association between uncoupling protein polymorphisms (UCP2-UCP3) and energy metabolism/obesity in Pima Indians. Hum Mol Genet 1998;7:1431-5. Abstract

[39]. Busfield F, Duffy DL, Kesting JB, et al. A genomewide search for type 2 diabetes-susceptibility genes in indigenous

Australians. Am J Hum Genet 2002;70:349-57. Abstract
[40]. Di Paola R, Frittitta L, Miscio G, et al. A variation in 3'UTR of *hPTP1B* increases specific gene expression and associates with insulin resistance. Am J Hum Genet 2002;70:806-12. Abstract
[41]. Lindgren CM, Mahtani MM, Widén E, et al. Genomewide search for type 2 diabetes mellitus susceptibility loci in Finnish families: the Botnia study. Am J Hum Genet 2002;70:509-16. Abstract
[42]. Horikawa Y, Oda N, Cox NJ, et al. **Genetic** variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. Nat Genet 2000;26:163-75. Abstract
[43]. Vionnet N, Hani EH, Dupont S, et al. Genomewide search for type 2 diabetes-susceptibility genes in French Whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2-diabetes locus on chromosome 1q21-q24. Am J Hum Genet 2000;67:1470-80. Abstract
[44]. Ghosh S, Watanabe RM, Valle TT, et al. The Finland-United States investigation of non-insulin dependent diabetes mellitus **genetics** (FUSION) study: I. an autosomal genome scan for genes that predispose to type 2 diabetes. Am J Hum Genet 2000;67:1174-85. Abstract
[45]. Watanabe RM, Ghosh S, Langefeld CD, et al. The Finland-United States Investigation of non-insulin-dependent diabetes mellitus **genetics** (FUSION) study: II. an autosomal genome scan for diabetes-related quantitative-trait loci. Am J Hum Genet 2000;67:1186-200. Abstract
[46]. Stone LM, Kahn SE, Fujimoto WY, Deeb SS, Porte Jr. D. A variation at position −30 of the beta-cell glucokinase gene promoter is associated with reduced beta-cell function in middle-aged Japanese-American men. Diabetes 1996;45:422-8. Abstract
[47]. Hart LM, Stolk RP, Dekker JM, et al. Prevalence of variants in candidate genes for type 2 diabetes mellitus in the Netherlands: the Rotterdam study and the Hoorn study. J Clin Endocrinol Metab 1999;84:1002-6. Full Text
[48]. Reis AF, Ye W-Z, Dubois-Laforgue D, Bellanne-Chantelot C, Timsit J, Velho G. Association of a variant in exon 31 of the sulfonylurea receptor 1 (SUR1) gene with type 2 diabetes mellitus in French Caucasians. Hum Genet 2000;107:138-44. Abstract
[49]. Altshuler D, Hirschhorn JN, Klannemark M, et al. The common PPAR gamma Pro12Ala polymorphism is associated with decreased **risk** of type 2 diabetes. Nat Genet 2000;26:76-80. Abstract
[50]. Soro A, Pajukanta P, Lilja HE, et al. Genome scans provide evidence for low-HDL-C loci on chromosomes 8q23, 16q24.1-24.2, and 20q13.11 in Finnish families. Am J Hum Genet 2002;70:1333-40. Abstract
[51]. Arya R, Duggirala R, Almasy L, et al. Linkage of high-density lipoprotein-cholesterol concentrations to a locus on chromosome 9p in Mexican Americans. Nat Genet 2002;30:102-5. Abstract
[52]. Peacock JM, Arnett DK, Atwood LD, et al. Genome scan for quantitative trait loci linked to high-density lipoprotein cholesterol: the NHLBI Family Heart Study. Arterioscler Thromb Vasc Biol 2001;21:1823-8. Abstract
[53]. Klos KL, Kardia SLR, Ferrell RE, Turner ST, Boerwinkle E, Sing CF. Genome-wide linkage analysis reveals evidence of multiple regions that influence variation in plasma lipid and apolipoprotein levels associated with **risk** of coronary heart disease. Arterioscler Thromb Vasc Biol 2001;21:971-8. Abstract
[54]. Wang XL, Rainwater DL, VandeBerg JF, Mitchell BD, Mahaney MC. **Genetic** contributions to plasma total antioxidant activity. Arterioscler Thromb Vasc Biol 2001;21:1190-5. Abstract
[55]. Smith SC, Greenland P, Grundy SM. AHA Conference Proceedings: Prevention Conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention. Executive Summary. Circulation 2000;101:111-6. Citation
[56]. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using **risk** factor categories. Circulation 1998;97:1837-47. Abstract
[57]. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executuve summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486-97. Citation
[58]. Gertler MM, White PD. Coronary heart disease in young adults: a multidisciplinary study. Cambridge (MA): Harvard University Press; 1954.
[59]. Thomas CB, Cohen BH. The familial occurrence of hypertension and coronary artery disease with observations concerning obesity and diabetes. Ann Intern Med 1955;42:90-127.
[60]. Rose G. Familial patterns in ischaemic heart disease. Br J Prev Soc Med 1964;18:75-80.
[61]. Slack J, Evans KA. The increased **risk** of death from ischaemic heart disease in first-degree relatives of 121 men and 96 women with ischaemic heart disease. J Med Genet 1966;3:239-57.
[62]. Rissanen AM. Familial occurrence of coronary heart disease: effect of age at diagnosis. Am J Cardiol 1979;44:60-6. Abstract
[63]. Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining **risk** of future disease. J Chron Dis 1986;39:809-21.

[64]. Silberberg JS, Wlodarczyk J, Fryer J, Robertson R, Hensley MJ. **Risk** associated with various definitions of family history of coronary heart disease. The Newcastle Family History Study II. Am J Epidemiol 1998;147:1133-9. Abstract
[65]. Nora JJ, Lortscher RH, Spangler RD, Nora AH, Komberling WJ. Genetic-epidemiologic study of early-onset ischemic heart disease. Circulation 1980;61:503-8. Abstract
[66]. Brown DW, Giles WH, Burke W, Greenlund KJ, Croft JB. Familial aggregation of early-onset myocardial infarction. Community Genet 2002;5:232-8.
[67]. Frielander Y, Kark JD, Stein Y. Family history of myocardial infarction as an independent **risk** factor for coronary heart disease. Br Heart J 1985;53:382-7. Abstract
[68]. Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring JE. Maternal and paternal history of myocardial infarction and **risk** of cardiovascular disease in men and women. Circulation 2001;104:393-8. Abstract
[69]. Sholtz RI, Rosenman RH, Brand RJ. The relationship of reported parental history to the incidence of coronary heart disease in the Western Collaborative Group Study. Am J Epidemiol 1975;102:350-6. Abstract
[70]. Colditz GA, Stampfer MJ, Willett WC, Rosner B, Speizer FE, Hennekens CH. A prospective study of parental history of myocardial infarction and coronary heart disease in women. Am J Epidemiol 1986;123:48-58. Abstract
[71]. Khaw KT, Barrett-Connor E. Family history of heart attack: A modifiable **risk** factor? Circulation 1986;74:239-44. Abstract
[72]. Schildkraut JM, Myers RH, Cupples LA, Kiely DK, Kannel WB. Coronary **risk** associated with age and sex of parental heart disease in the Framingham Study. Am J Cardiol 1989;64:555-9. Abstract
[73]. Phillips AN, Shaper AG, Pocock SJ, Walker M. Parental death from heart disease and the **risk** of heart attack. Eur Heart J 1988;9:243-51. Abstract
[74]. Hopkins PN, Williams RR, Kuida H, et al. Family history as an independent **risk** factor for incident coronary artery disease in a high-risk cohort in Utah. Am J Cardiol 1988;62:703-7. Abstract
[75]. Colditz GA, Rimm EB, Giovannucci E, Stampfer MJ, Rosner B, Willett WC. A prospective study of parental history of myocardial infarction and coronary artery disease in men. Am J Cardiol 1991;67:933-8. Abstract
[76]. De Jong SC, Stehouwer CDA, Mackaay AJC, et al. High prevalence of hyperhomocysteinemia and asymptomatic vascular disease in siblings of young patients with vascular disease and hyperhomocysteinemia. Arterioscler Thromb Vasc Biol 1997;17:2655-62. Abstract
[77]. Margaglione M, Cappucci G, Colaizzo D, Vecchione G, Grandone E, Di Minno G. C-reactive protein in offspring is associated with the occurrence of myocardial infarction in first-degree relatives. Arterioscler Thromb Vasc Biol 2000;20:198-203. Abstract
[78]. Mills JD, Mansfield MW, Grant PJ. Tissue plasminogen activator, fibrin D-dimer, and insulin resistance in the relatives of patients with premature coronary artery disease. Arterioscler Thromb Vasc Biol 2002;22:704-9. Abstract
[79]. Kareinen A, Viitanen L, Halonen P, Lehto S, Laakso M. Cardiovascular **risk** factors associated with insulin resistance cluster in families with early-onset coronary heart disease. Arterioscler Thromb Vasc Biol 2001;21:1346-52. Abstract
[80]. Kee F, Tiret L, Robo JY, et al. Reliability of reported family history of myocardial infarction. BMJ 1993;307:1528-30. Abstract
[81]. Bensen JT, Liese AD, Rushing JT, et al. Accuracy of proband reported family history: the NHLBI Family Heart Study (FHS). Genet Epidemiol 1999;17:141-50. Abstract
[82]. Williams RR, Hunt SC, Heiss G, et al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the Health Family Tree Study and the NHLBI Family Heart Study). Am J Cardiol 2001;87:129-35. Full Text
[83]. Scheuner MT, Wang S-J, Raffel LJ, Larabell SK, Rotter JI. Family history: a comprehensive **genetic risk** assessment method for the chronic conditions of adulthood. Am J Med Genet 1997;71:315-24. Abstract
[84]. Lamarche B, Lemieux I, Després JP. The small, dense LDL phenotype and the **risk** of coronary heart disease: Epidemiology, pathophysiology and therapeutic aspects. Diabetes Metab 1999;25:199-211. Abstract
[85]. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. JAMA 1996;276:875-81. Abstract
[86]. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense LDL particles and the **risk** of ischemic heart disease: prospective results from the Québec Cardiovascular Study. Circulation 1997;95:69-75. Abstract
[87]. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and **risk** of myocardial infarction. JAMA 1996;276:882-8. Abstract
[88]. St-Pierre AC, Ruel IL, Cantin B, et al. Comparison of various electrophoretic characteristics of LDL particles and their relationship to the **risk** of ischemic heart disease. Circulation 2001;104:2295-9. Abstract
[89]. Superko HR. Small, dense LDL subclass phenotype B: issues for clinicians. Curr Atheroscler Rep 1999;1:50-7. Abstract

[90]. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65. Abstract
[91]. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001;285:2481-5. Abstract
[92]. Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative Observational Study. JAMA 2002;288:980-7. Abstract
[93]. Danesh J, Lewington S. Plasma homocysteine and coronary heart disease: systematic review of published epidemiological studies. J Cardiovasc Risk 1998;5:229-32. Citation
[94]. Tawacol A, Omland T, Gerhard M, Wu JT, Creager MA. Hyperhomocysteinemia is associated with impaired endothelial-dependent vasodilation in humans. Circulation 1997;95:1191-211.
[95]. Mangoni AA, Jackson SH. Homocysteine and cardiovascular disease: current evidence and future prospects. Am J Med 2002;112:556-65. Full Text
[96]. Desouza C, Keebler M, McNamara DB, Fonseca V. Drugs affecting homocysteine metabolism: impact on cardiovascular risk. Drugs 2002;62:605-16. Abstract
[97]. Ubbink JB. The role of vitamins in the pathogenesis and treatment of hyperhomocysteinemia. J Inherit Metab Dis 1997;20:315-25. Abstract
[98]. Malinow MR, Bostrom AG, Krauss RM. Homocyst(e)ine, diet, and cardiovascular diseases: a statement for healthcare professionals from the nutrition committee, American Heart Association. Circulation 1999;99:178-82. Citation
[99]. Brattstrom LE, Israelsson B, Norrving B, et al. Impaired homocysteine metabolism in early-onset cerebral and peripheral occlusive arterial disease: effects of pyridoxine and folic acid treatment. Atherosclerosis 1990;81:51-60. Abstract
[100]. Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss heart study: a randomized controlled trial. JAMA 2002;288:973-9. Abstract
[101]. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke (VISP) randomized controlled trial. JAMA 2004;291:565-75. Abstract
[102]. Baker F, Picton D, Blackwood S, et al. Blinded comparison of folic acid and placebo in patients with ischemic heart disease: an outcome trial. Circulation 2002;106(Suppl II):741S.
[103]. Stein JH, Rosenson RS. Lipoprotein Lp(a) excess and coronary heart disease. Arch Intern Med 1997;157:1170-6. Abstract
[104]. Jenner JL, Ordovas I, Lamon-Fava S, et al. Effects of age, sex and menopausal status on plasma lipoprotein(a) levels: The Framingham Offspring Study. Circulation 1993;87:1135-41. Abstract
[105]. Berg K. Lp(a) lipoprotein: a monogenic risk factor for cardiovascular disease. In: GoldbourtU, de FaireU, BergK, editors. Genetic factors in coronary heart disease Boston: Kluwer Academic Publishers; 1994. p. 275-87.
[106]. Kraft HG, Lingenhel A, Kochl S, et al. Apolipoprotein(a) kringle IV repeat number predicts risk for coronary heart disease. Arterioscler Thromb Vasc Biol 1996;16:713-9. Abstract
[107]. Marcovina SM, Kochinsky ML. Lipoprotein(a) concentration and apolipoprotein(a) size: a synergistic role in advanced atherosclerosis? Circulation 1999;100:1151-3. Citation
[108]. Gurakar A, Hoeg JM, Kostner G, Papadopoulos NM, Brewer Jr. HB. Levels of lipoprotein(a) decline with neomycin and niacin treatment. Atherosclerosis 1985;57:293-301. Abstract
[109]. Temme EH, Mensink RP, Hornstra G. Comparison of the effects of diets enriched in lauric, palmitic, or oleic acids on serum lipids and lipoproteins in healthy women and men. Am J Clin Nutr 1996;63:897-903. Abstract
[110]. Thomas TR, Ziogas G, Harris WS. Influence of fitness status on very-low density lipoproteins subfractions and lipoprotein(a) in men and women. Metabolism 1997;46:1178-83. Abstract
[111]. Espeland MA, Marcovina SM, Miller V, et al. Effect of postmenopausal hormone therapy on lipoprotein(a) concentration. PEPI Investigators. Postmenopausal Estrogen/Progestin Interventions. Circulation 1998;97:979-86. Abstract
[112]. Zmuda JM, Thompson PD, Dickenson R, Bausserman LL. Testosterone decreases lipoprotein(a) in men. Am J Cardiol 1996;77:1244-7. Abstract
[113]. Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. JAMA 2000;283:1845-52. Abstract
[114]. Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). JAMA 1995;274:1771-4. Abstract
[115]. Krauss RM. Dense low-density lipoproteins and coronary artery disease. Am J Cardiol 1995;75:53B-7B. Abstract
[116]. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low density lipoprotein subclass patterns

and risk of myocardial infarction. JAMA 1988;260:917-21. Abstract
[117]. Griffin BA, Freeman DJ, Tait GW, et al. Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: relative contribution of small, dense LDL to coronary heart disease risk. Atherosclerosis 1994;106:241-53. Abstract
[118]. Dreon DM, Fernstrom HA, Williams PT, Krauss RM. LDL subclass phenotypes and lipoprotein response to a low-fat, high-carbohydrate diet in women. Arterioscler Thromb Vasc Biol 1997;17:707-14. Abstract
[119]. Superko HR, Krauss RM. Differential effects of nicotinic acid in subjects with different LDL subclass phenotypes. Atherosclerosis 1992;95:69-76. Abstract
[120]. Sakai T, Kamanna VS, Kashyap ML. Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. Arteerioscler Thromb Vasc Biol 2001;21:1783-9.
[121]. Superko HR, Haskell WL, Krauss RM. Association of lipoprotein subclass distribution with use of selective and non-selective beta-blocker medications in patients with coronary heart disease. Atherosclerosis 1993;101:1-8. Abstract
[122]. Minihane AM, Khan S, Leigh-Firbank EC, et al. ApoE polymorphism and fish oil supplementation in subjects with atherogenic lipoprotein phenotype. Arterioscler Thromb Vasc Biol 2000;20:117-28. Abstract
[123]. Ito MK. Niacin-based therapy for dyslipidemia: past evidence and future advances. Am J Manag Care 2002;8 (Suppl):S315-22. Abstract
[124]. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. JAMA 2002;287:356-9. Abstract
[125]. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403. Abstract
[126]. Backes JM, Howard PA, Moriarty PM. Role of C-reactive protein in cardiovascular disease. Ann Pharmacother 2004;38:110-8. Abstract
[127]. Ridker PM, Morrow DA. C-reactive protein, inflammation, and coronary risk. Cardiol Clin 2003;21:315-25. Full Text

[128]. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. Circulation 1999;100:230-5. Abstract
[129]. Maison P, Mennen L, Sapinho D, et al. A pharmacoepidemiological assessment of the effect of statins and fibrates on fibrinogen concentration. Atherosclerosis 2002;160:155-60. Abstract
[130]. Harper CR, Jacobson TA. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. Arch Intern Med 2001;161:2185-92. Abstract
[131]. Online Mendelian Inheritance in Man. OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2000. Available at: http://www.ncbi.nlm.nih.gov/omim/ . Accessed April 2003.
[132]. Scheuner MT, Yoon P, Khoury MJ. Contribution of Mendelian disorders to common chronic disease: opportunities for recognition, intervention and prevention. Am J Med Genet 2004;125C:50-65. Abstract
[133]. Glazier AM, Nadeau JH, Aitman TJ. Finding genes that underlie complex traits. Science 2002;298:2345-9. Abstract
[134]. Kuivenhoven JA, Jukema JW, Zwinderman AH, et al. The role of a common variant of the cholesterol ester transfer protein gene in the progression of coronary atherosclerosis. N Engl J Med 1998;338:86-93. Abstract
[135]. Nieminen MS, Mattila KJ, Aalto-Setala K, et al. Lipoproteins and their genetic variation in subjects with and without angiographically verified coronary disease. Arteriosclerosis Thromb 1992;12:58-69.
[136]. Eto M, Watanable K, Makino I. Increased frequencies of apolipoprotein E2 and E4 alleles in patients with ischemic heart disease. Clin Genet 1989;39:183-9. Abstract
[137]. Cumming AM, Robertson F. Polymorphism at the apoE locus in relation to risk of coronary heart disease. Clin Genet 1984;25:310-3. Abstract
[138]. Tikkanen MJ, Huttunen JK, Ehnholm C, Pietinen P. Apolipoprotein E4 homozygosity predisposes to serum cholesterol elevation during high fat diet. Arteriosclerosis 1990;10:285-8. Abstract
[139]. Lopez-Miranda J, Ordovás JM, Mata P, et al. Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. J Lipid Res 1994;35:1965-75. Abstract
[140]. Ordovás JM, Lopez-Miranda JM, Mata P, Perez-Jimenez F, Lichtenstein AH, Schaefer EJ. Gene-diet interaction in determining plasma lipid response to dietary intervention. Atherosclerosis 1995;118:S11-27. Abstract
[141]. Campos H, D'Angostino M, Ordovás JM. Gene-diet interactions and plasma lipoproteins: role of apolipoprotein E and habitual saturated fat intake. Genet Epidemiol 2001;20:117-28. Abstract
[142]. Denke MA, Adams-Huet B, Nguyen AT. Individual cholesterol variation in response to a margarine- or butter-based diet. JAMA 2000;284:2740-7. Abstract
[143]. Hokanson JE, Austin MA. Plasma triglyceride is a risk factor for cardiovascular disease independent of high-density

lipoprotein cholesterol: a meta analysis of population based studies. J Cardiovasc Risk 1996;3:213-9. Abstract
[144]. Roses AD. Apolipoprotein E affects the rate of Alzheimer disease expression: beta-amyloid burden is a secondary consequence dependent on APOE genotype and duration of disease. J Neuropathol Exp Neurol 1994;53:429-37. Citation
[145]. American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer Disease. Statement on use of apolipoprotein E testing for Alzheimer disease. JAMA 1995;274:1627-9. Abstract
[146]. Brattstrom L, Wilcken DE, Ohrvik J, Brudin L. Common methylenetetrahydrolfolate reductase gene mutation leads to hyperhomocysteinemia but not to vascular disease: the result of a meta-analysis. Circulation 1998;98:2520-6. Abstract
[147]. Klerk M, Verhoef P, Clarke R, et al. MTHFR 677C-T polymorphism and risk of coronary heart disease: a meta-analysis. JAMA 2002;288:2023-31. Abstract
[148]. American Society of Human Genetics/American College of Medical Genetics Test and Technology Transfer Committee Working Group. ASHG/ACMG Statement: measurement and use of total plasma homocysteine. Am J Hum Genet 1998;63:1541-3. Abstract
[149]. Psaty BM, Smith NL, Lemaitre RN, et al. Hormone replacement therapy, prothrombotic mutations, and the risk of incident nonfatal myocardial infarction in postmenopausal women. JAMA 2001;285:906-13. Abstract
[150]. Sen-Banerjee S, Siles X, Campos H. Tobacco smoking modifies association between Gln-Arg192 polymorphism of human paraoxonase gene and risk of myocardial infarction. Arterioscler Thromb Vasc Biol 2000;20:2120-6. Abstract
[151]. Moshfegh K, Wuillemin WA, Redondo M, et al. Association of two silent polymorphisms of platelet glycoprotein Ia/IIa receptor with risk of myocardial infarction. Lancet 1999;353:351-4. Abstract
[152]. US Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 2002;136:157-60. Abstract
[153]. Dwyer JH, Allayee H, Dwyer KM, et al. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. N Engl J Med 2004;350:29-37. Abstract
[154]. Psaty BM, Smith NL, Heckbert SR, et al. Diuretic therapy, the alpha-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. JAMA 2002;287:1680-9. Abstract
[155]. Hines LM, Stampfer MJ, Ma J, et al. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. N Engl J Med 2001;344:549-55. Abstract
[156]. Herrington DM, Howard TD, Hawkins GA, et al. Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. N Engl J Med 2002;346:967-74. Abstract
[157]. McKinnon WC, Baty BJ, Bennett RL, et al. Predisposition genetic testing for late-onset disorders in adults: a position paper of the National Society of Genetic Counselors. JAMA 1997;278:1217-20. Citation
[158]. Kip KE, McCreath HE, Roseman JM, Hulley SB, Schreiner PJ. Absence of risk factor change in young adults after family heart attack or stroke: the CARDIA study. Am J Prev Med 2002;22:258-66. Abstract
[159]. Knutsen SF, Knutsen R. The Tromso survey: the family intervention study—the effect of intervention on some coronary risk factors and dietary habits, a 6-year follow-up. Prev Med 1991;20:197-212. Abstract
[160]. Randomised controlled trial evaluating cardiovascular screening and intervention in general practice: principal results of British family heart study. BMJ 1994;308:313-20. Abstract
[161]. Pyke SDM, Wood DA, Kinmonth AL, Thompson SG. Change in coronary risk and coronary risk factor levels in couples following lifestyle intervention. Arch Fam Med 1997;6:354-60. Abstract
[162]. Arnoff SL, Bennett PH, Gorden P, Rushforth N, Miller M. Unexplained hyperinsulinemia in normal and 'prediabetic' Pima Indians compared with normal Caucasians. Diabetes 1977;26:827-40. Abstract
[163]. Sharp PS, Mohan V, Levy JC, Mather HM, Kohner EM. Insulin resistance in patients of Asian Indian and European origin with non-insulin dependent diabetes. Horm Metab Res 1987;19:84-5. Citation
[164]. Rosendaal FR, Siscovick DS, Schwartz SM, et al. Factor V Leiden (resistance to activated protein C) increases the risk of myocardial infarction in young women. Blood 1997;89:2817-21. Abstract
[165]. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study. Circulation 1995;92:2157-62. Abstract
[166]. Bielak LF, Rumberger JA, Sheedy PF, Schwartz RS, Peyser PA. Probabilistic model for prediction of angiographically defined obstructive coronary artery disease using electron beam computed tomography calcium score strata. Circulation 2000;102:380-5. Abstract
[167]. Nallamothu BK, Saint S, Rubenfire M, Fendrick AM. Electron beam computed tomography in the diagnosis of obstructive coronary artery disease. J Am Coll Cardiol 2001;37:689-90. Citation
[168]. Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries: 19-month follow-up of 1173 asymptomatic subjects. Circulation 1996;93:1951-3. Abstract
[169]. Secci A, Wong N, Tang W, Wang S, Doherty T, Detrano R. Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. Circulation 1997;96:1122-9. Abstract

[170]. Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased **risk** of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation 2000;101:850-5. Abstract
[171]. Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol 1996;27:285-90. Abstract
[172]. He ZX, Hedrick TD, Pratt CM, et al. Severity of coronary artery calcification by electron beam tomography predicts silent myocardial ischemia. Circulation 2000;101:244-51. Abstract
[173]. Raggi P, Cooll B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. Am Heart J 2001;141:372-82.
[174]. Wong ND, Detrano RC, Diamond G, et al. Does coronary artery screening by electron beam computed tomography motivate potentially beneficial lifestyle behaviors? Am J Cardiol 1996;78:1220-3. Abstract
[175]. Blankenhorn DH, Nessim SA, Johnson R, et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987;247:3233-40. Abstract
[176]. Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med 1993;119:969-76. Abstract
[177]. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990;323:1289-98. Abstract
[178]. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9. Abstract
[179]. Jukema JW, Bruschke AVG, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). Circulation 1995;91:2528-40. Abstract
[180]. MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). Lancet 1994;344:633-8. Abstract
[181]. Kreisberg RA. Cholesterol-lowering and coronary atherosclerosis: good news and bad news. Am J Med 1996;101:455-8. Citation
[182]. Miller M. Niacin as a component of combination therapy for dyslipidemia. Mayo Clin Proc 2003;78:735-42. Abstract
[183]. Panagiotakos DB, Pitsavos C, Chrysohoou C, et al. Effect of leisure time physical activity on blood lipid levels: the ATTICA study. Coron Artery Dis 2003;14:533-9.
[184]. Chung BH, Doran S, Liang P, et al. Alcohol-mediated enhancement of postprandial lipemia: a contributing factor to an increase in plasma HDL and a decrease in **risk** of cardiovascular disease. Am J Clin Nutr 2003;78:391-9. Abstract
[185]. Schwartz ML. Severe reversible hyperglycemia as a consequence of niacin therapy. Arch Intern Med 1993;153:2050-2. Abstract
[186]. Smith CC, Bernstein LI, Davis RB, Rind DM, Shmerling RH. Screening for statin-related toxicity: the yield of transaminase and creatinine kinase measurements in a primary care setting. Arch Intern Med 2003;163:657-9. Abstract